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 2/3/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

13292703   BIOSIS NO.: 200100499852
Antithrombotic agent and anti-von willebrand factor monoclonal antibody.
AUTHOR: Nagano Mitsuyo(a); Yamamoto Hiroshi; Kito Morikazu; Yoshimoto
  Ryota; Kobayashi Tsuyoshi
AUTHOR ADDRESS: (a)Kawasaki**Japan
JOURNAL: Official Gazette of the United States Patent and Trademark Office
Patents  1249 (4):pNo Pagination Aug. 28, 2001
MEDIUM: e-file
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ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

2/3/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12826178 BIOSIS NO.: 200100033327
Activation of cerebral function by CS-932, a functionally selective M1 partial agonist: Neurochemical characterization and pharmacological studies.
AUTHOR: Iwata Nobuyoshi; Kozuka Masao; Hara Takao; Kaneko Tsugio(a); Tonohiro Toshiyuki; Sugimoto Masahiko; Niitsu Yoichi; Kondo Yusuke; Yamamoto Tsuneyuki; Sakai Jun-ichi; **Nagano Mitsuo**
AUTHOR ADDRESS: (a)Neuroscience and Immunology Research Laboratories, Sankyo Co., Ltd., 2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo, 140-8710: tkanek@shina.sankyo.co.jp**Japan
JOURNAL: Japanese Journal of Pharmacology 84 (3):p266-280 November, 2000
MEDIUM: print
ISSN: 0021-5198
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

2/3/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11747657 BIOSIS NO.: 199800528353
Central activation by CS-932, a functionally relative M1 agonist.
AUTHOR: Kaneko Tsugio(a); Tonohiro Toshiyuki(a); Hara Takao(a); Sakai Junichi; **Nagano Mitsuo**; Iwata Nobuyoshi(a
AUTHOR ADDRESS: (a)Neurosci. Res. Lab., Sankyo Co. Ltd., Shinagawa-ku, Tokyo 140-8710**Japan
JOURNAL: Neuroscience Research Supplement (22):pS361 1998
CONFERENCE/MEETING: 21st Annual Meeting of the Japan Neuroscience Society and the First Joint Meeting of the Japan Neuroscience Society and the Japanese Society for Neurochemistry Tokyo, Japan September 21-23, 1998
SPONSOR: Japan Neuroscience Society
ISSN: 0921-8696
RECORD TYPE: Citation
LANGUAGE: English

2/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11126919 BIOSIS NO.: 199799748064
Anti-thrombotic effects and bleeding risk of AJvW-2, a monoclonal antibody against human von Willebrand factor.
AUTHOR: Kageyama Shunsuke; Yamamoto Hiroshi(a); **Nagano Mitsuyo**; Arisaka Harumi; Kayahara Takashi; Yoshimoto Ryota
AUTHOR ADDRESS: (a)Life Sci. Lab., Central Res. Lab., Ajinomoto Co. Ltd., 214 Maeda-cho, Totsuka-ku, Yokohama 244**Japan
JOURNAL: British Journal of Pharmacology 122 (1):p165-171 1997
ISSN: 0007-1188
RECORD TYPE: Abstract
LANGUAGE: English

2/3/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09992326 BIOSIS NO.: 199598447244
Early administration of YT-146, an adenosine A-2 receptor agonist, inhibits neointimal thickening after rat femoral artery endothelium injury.
AUTHOR: Takiguchi Yoshiharu(a); **Nagano Mitsuyo**; Ikeda Yasuhiko; Nakashima Mitsuyoshi
AUTHOR ADDRESS: (a)Dep. Pharmacol., Hamamatsu Univ. Sch. Med., 3600 Handa-cho, Hamamatsu 431-31**Japan
JOURNAL: European Journal of Pharmacology 281 (2):p205-207 1995
ISSN: 0014-2999
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

2/3/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09802663 BIOSIS NO.: 199598257581
Inhibitory effects of ketanserin on thrombus formation and neointimal thickening in the rat femoral artery.
AUTHOR: Ikeda Yasuhiko; Takiguchi Yoshiharu; **Nagano Mitsuyo**; Kikuchi Shinji; Umemura Kazuo; Nakashima Mitsuyoshi
AUTHOR ADDRESS: Dep. Pharmacol., Hamamatsu University Sch. Med., Hamamatsu 431-31**Japan
JOURNAL: Japanese Journal of Pharmacology 67 (SUPPL. 1):p113P 1995
CONFERENCE/MEETING: 68th Annual Meeting of the Japanese Pharmacological Society Nagoya, Japan March 25-28, 1995
ISSN: 0021-5198
RECORD TYPE: Citation
LANGUAGE: English

2/3/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09802501 BIOSIS NO.: 199598257419
Inhibitory effect of an adenosine A-2 agonist on neointimal thickening after rat femoral artery injury.
AUTHOR: Takiguchi Yoshiharu; Ikeda Yasuhiko; **Nagano Mitsuyo**; Umemura Kazuo; Nakashima Mitsuyoshi
AUTHOR ADDRESS: Dep. Pharmacol., Hamamatsu Univ. Sch. Med., Hamamatsu 431-31**Japan
JOURNAL: Japanese Journal of Pharmacology 67 (SUPPL. 1):p71P 1995
CONFERENCE/MEETING: 68th Annual Meeting of the Japanese Pharmacological Society Nagoya, Japan March 25-28, 1995
ISSN: 0021-5198
RECORD TYPE: Citation
LANGUAGE: English

2/3/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09298312 BIOSIS NO.: 199497306682
Sites of action of CS-722, a newly synthesized centrally acting muscle

relaxant.
AUTHOR: Tanabe Mitsuo(a); Ishizuka Hitoshi; Murayama Takako; Kaneko Tsugio; Tonohiro Toshiyuki(a); Sakai Jun-Ichi(a); **Nagano Mitsuo**; Sasahara Kunihiro; Iwata Nobuyoshi(a
AUTHOR ADDRESS: (a)Neurosci. Lab., Sankyo Co. Ltd., Tokyo 140**Japan
JOURNAL: Japanese Journal of Pharmacology 64 (SUPPL. 1):p208P 1994
CONFERENCE/MEETING: 67th Annual Meeting of the Japanese Pharmacological Society Kyoto, Japan March 21-24, 1994
ISSN: 0021-5198
RECORD TYPE: Citation
LANGUAGE: English

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? s ajvw? and (antibod? or hybridoma? or immunoglobulin?) and willebrand
              45  AJVW?
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           48044  HYBRIDOMA?
          638392  IMMUNOGLOBULIN?
           34473  WILLEBRAND
      S3      40  AJVW? AND (ANTIBOD? OR HYBRIDOMA? OR IMMUNOGLOBULIN?) AND
                  WILLEBRAND
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 4/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.
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14341552 BIOSIS NO.: 200300335581
Shielding the Front A1 Domain Pocket of von **Willebrand** Factor Inhibits Its Binding to Platelet Glycoprotein Ibalpha.
AUTHOR: Bonnefoy Arnaud(a); Yamamoto Hiroshi(a); Thys Chantal(a); Kito Morikazu(a); Vermylen Jos(a); Hoylaerts Marc F(a)
AUTHOR ADDRESS: (a)Center for Molecular and Vascular Biology, KULeuven, Leuven, Belgium**Belgium
JOURNAL: Blood 100 (11):pAbstract No 981 November 16 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Platelet adhesion to damaged vessel wall and shear-induced platelet aggregation necessitate binding of the von **Willebrand** Factor (vWf) A1 domain to platelet GPIbalpha. Blocking this interaction represents a promising approach to the treatment of arterial thrombosis. Comparison of amino acid sequences of the vWf A1 domain in several species, expressing vWf recognized by the blocking monoclonal **antibody AJvW**-2, suggested nine residues (H563, I566, D570, A581, V584, A587, R616, A618 and M622) to contribute to the epitope for **AJvW**-2 and/or to be part of the GPIbalpha binding site. GST/human vWf A1 fusion proteins, in which these amino acids were mutated to their murine counterpart, were tested for their capacity to bind **AJvW**-2 or heparin, to interfere with botrocetin or ristocetin mediated vWf binding to GPIb, or to induce flow-dependent platelet tethering in a perfusion chamber. Thus, mutations H563R, I566L, D570A, and A587T, clustered on the outer surface of the A1 domain, dramatically impaired binding of **AJvW**-2 to A1. The H563R, I566L and D570A mutations also impaired the binding of heparin, which competes with **AJvW**-2 for binding to A1. Perfusion studies revealed that H563, I566, D570, R616 and A618 take part in GPIbalpha binding, their mutation impairing platelet recruitment. In agreement with the surface distribution of vWf type 2M

mutations, this study demonstrates overlapping of the epitope for **AJvW**-2 and the GPIbalpha binding site, located around the front pocket of the A1 domain and defined by strands beta3 and beta4 and helix alpha3, and provides a mechanistic basis for vWf neutralization by this **antibody**.

4/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

14125323 BIOSIS NO.: 200300119352
Shielding the front-strand beta3 of the von **Willebrand** factor A1 domain inhibits its binding to platelet glycoprotein Ibalpha.
AUTHOR: Bonnefoy Arnaud; Yamamoto Hiroshi; Thys Chantal; Kito Morikazu; Vermylen Jos; Hoylaerts Marc F(a)
AUTHOR ADDRESS: (a)Center for Molecular and Vascular Biology, University of Leuven, Herestraat 49, Campus Gasthuisberg, B-3000, Leuven, Belgium** Belgium E-Mail: marc.hoylaerts@med.kuleuven.ac.be
JOURNAL: Blood 101 (4):p1375-1383 February 15 2003 2003
MEDIUM: print
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Platelet adhesion to damaged vessel wall and shear-induced platelet aggregation necessitate binding of the von **Willebrand** factor (VWF) A1 domain to platelet GPIbalpha. Blocking this interaction represents a promising approach to the treatment of arterial thrombosis. Comparison of amino acid sequences of the VWF A1 domain in several species, expressing VWF recognized by the blocking monoclonal **antibody AJvW**-2, suggested 9 residues (His563, Ile566, Asp570, Ala581, Val584, Ala587, Arg616, Ala618, and Met622) to contribute to the epitope for **AJvW**-2 or to be part of the GPIbalpha-binding site. Glutathione-S-transferase (GST)-human VWF A1 fusion proteins, in which these amino acids were mutated to their murine counterparts, were tested for their capacity to bind **AJvW**-2 or heparin, to interfere with botrocetin- or ristocetin-mediated VWF binding to GPIb, or to induce flow-dependent platelet tethering in a perfusion chamber. Thus, mutations His563Arg, Ile566Leu, Asp570Ala, and Ala587Thr, clustered on the outer surface of the A1 domain, dramatically impaired binding of **AJvW**-2 to A1. The His563Arg, Ile566Leu, and Asp570Ala mutations also impaired the binding of heparin, which competes with **AJvW**-2 for binding to A1. Perfusion studies revealed that His563, Ile566, Asp570, Arg616, and Ala618 take part in GPIbalpha binding, their mutation-impairing platelet recruitment. In agreement with the surface distribution of VWF type 2M mutations, this study demonstrates overlapping of the epitope for **AJvW**-2 and the GPIbalpha-binding site, located around the front pocket of the A1 domain and defined by strands beta3, beta4, and helix alpha3, and it provides a mechanistic basis for VWF neutralization by this **antibody**.

4/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13022298 BIOSIS NO.: 200100229447
Real-time analysis of the interaction of platelets with immobilized thrombospondin under flow conditions.
AUTHOR: Onitsuka Ichiro; Jung Stephanie M; Ikeda Hisao; Imaizumi Tsutomu; Moroi Masaaki(a)
AUTHOR ADDRESS: (a)Department of Protein Biochemistry, Institute of Life

Science, Kurume University, 2432-3 Aikawa-machi, Kurume, Fukuoka, 839-0861: moroi@mbox.lsi.kurume-u.ac.jp**Japan
JOURNAL: Thrombosis Research 101 (6):p455-465 March 15, 2001
MEDIUM: print
ISSN: 0049-3848
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The platelet granule protein (TS) is extracellularly secreted upon platelet activation and then binds to the platelet surface where it can interact with various adhesive proteins. Here, we have analyzed platelet interactions with a TS-coated surface under flow conditions, a model for platelet adhesion onto surface-bound TS under physiological conditions. Platelets exhibited temporary, very short-time adhesion on the TS surface, but no firm adhesion. This adhesion was inhibited by NNKY5-5 (anti-glycoprotein (GP) Ib **antibody**) and **AJvW-2** (anti-von **Willebrand** factor (vWF)), indicating that both platelet GP Ib and plasma vWF contribute to this interaction. **Antibodies** against platelet collagen receptor integrin alpha2beta1 had no significant effect. These results suggested that binding of vWF to TS is the first step in platelet interaction with the TS surface. By surface plasmon resonance spectroscopy, a dissociation constant (Kd) of 3.97 X 10-7 M was obtained for the binding reaction between immobilized TS and vWF. These results suggest the following model for platelet interaction with the TS surface under flow: plasma vWF first binds to the immobilized TS and then platelets interact with the TS-bound vWF. A low density of bound vWF would account for the observed weak interaction between TS and platelets under flow.

4/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13009153 BIOSIS NO.: 200100216302
A new approach to antiplatelet therapy: Inhibitor of GPIb/V/IX-vWF interaction.
AUTHOR: Ikeda Yasuo(a); Handa Makoto; Murata Mitsuru; Goto Shinya
AUTHOR ADDRESS: (a)Division of Hematology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582: yikeda@med.keio.au.jp**Japan
JOURNAL: Haemostasis 30 (Suppl 3):p44-52 February, 2000
MEDIUM: print
ISSN: 0301-0147
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Evidence has been presented that the interaction between von **Willebrand** factor (vWF) and its platelet membrane receptor, the GPIb/V/IX complex, plays an important role in the pathogenesis of arterial thrombosis. A monoclonal **antibody** against the A1 domain of vWF has been shown to inhibit thrombus formation in the animal model of arterial thrombosis. Based upon these findings, a new approach to treating arterial thrombosis has been proposed by intervening in the interaction between vWF and platelet.

4/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12775363 BIOSIS NO.: 200000528986
Anti-human von **Willebrand** factor monoclonal **antibody AJvW**
-2 prevents thrombus deposition and neointima formation after balloon injury in guinea pigs.
AUTHOR: Kageyama Shunsuke; Yamamoto Hiroshi(a); Yoshimoto Ryota
AUTHOR ADDRESS: (a)Developmental Research Laboratories, Pharmaceutical Research Laboratories, Ajinomoto Co, Inc, 1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, 210-8681**Japan
JOURNAL: Arteriosclerosis Thrombosis and Vascular Biology 20 (10):p 2303-2308 October, 2000
MEDIUM: print
ISSN: 1079-5642
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Immediately after angioplasty, platelet adhesion to the injured arterial wall and subsequent release of various mitogens may contribute to neointima formation. The purpose of this study was to evaluate the inhibitory effect of **AJvW**-2, a monoclonal **antibody** against human von **Willebrand** factor (vWF), on neointima formation in a guinea pig model. The carotid artery was injured with a balloon catheter, and **AJvW**-2 was administered by a single bolus injection. **AJvW**-2 dose-dependently prevented neointima formation 14 days after injury. Significant inhibition was observed at 1.8 mg/kg, at which dose significant inhibition of platelet aggregation was achieved for 2 days. By elastic-Masson staining, organized thrombi were observed in the neointimal lesion on day 14. The thrombus area was significantly correlated with neointimal thickness. Furthermore, thrombus deposition, immunostained for vWF and fibrin(ogen), was observed on the media immediately after balloon injury. **AJvW**-2 significantly reduced the deposition of both adhesive proteins and reduced the incidence of organized thrombus formation, which might affect subsequent neointima formation. However, the proliferation of cultured smooth muscle cells was not affected by **AJvW**-2. These results suggest that **AJvW**-2 prevents neointima formation by inhibition of initial platelet-mediated thrombus formation rather than by direct inhibition of smooth muscle cell proliferation.

4/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12220284 BIOSIS NO.: 199900515133
Effect of **AJvW**-2, anti-human von **Willebrand** factor (vWG) A1 domain MoAb, on vWF-dependent platelet aggregation following coronary stent implantation.
AUTHOR: Eto Koji(a); Isshiki Takaaki(a); Ochiai Masahiko(a); Takeshita Satoshi(a); Mitani Haruo(a); Tokuda Takahiro(a); Sato Tomohide(a); Yamamoto Hiroshi(a); Yoshimoto Ryota
AUTHOR ADDRESS: (a)Teikyo Univ., Tokyo**Japan
JOURNAL: Circulation 98 (17 SUPPL.):pI573 Oct. 27, 1998
CONFERENCE/MEETING: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998
SPONSOR: The American Heart Association
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English

4/7/7 (Item 7 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

12220241 BIOSIS NO.: 199900515090
von **Willebrand** factor-dependent platelet aggregation is enhanced during chest pain attacks in patients with unstable angina: Effect of **AJvW**-2, anti-vWF A1 domain **antibody** against unstable angina.
AUTHOR: Eto Koji(a); Isshiki Takaaki(a); Takeshita Satoshi; Ochiai Masahiko ; Sato Tomohide; Yamamoto Hiroshi; Yoshimoto Ryota
AUTHOR ADDRESS: (a)Teikyo Univ., Tokyo**Japan
JOURNAL: Circulation 98 (17 SUPPL.):pI561 Oct. 27, 1998
CONFERENCE/MEETING: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998
SPONSOR: The American Heart Association
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English

4/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11981122 BIOSIS NO.: 199900234435
AJvW-2, an anti-vWF monoclonal **antibody**, inhibits enhanced platelet aggregation induced by high shear stress in platelet-rich plasma from patients with acute coronary syndromes.
AUTHOR: Eto Koji(a); Isshiki Takaaki; Yamamoto Hiroshi; Takeshita Satoshi; Ochiai Masahiko; Yokoyama Naoyuki; Yoshimoto Ryota; Ikeda Yasuo; Sato Tomohide
AUTHOR ADDRESS: (a)Department of Medicine (Cardiology), Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi**Japan
JOURNAL: Arteriosclerosis Thrombosis and Vascular Biology 19 (4):p877-882 April, 1999
ISSN: 1079-5642
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The platelet aggregation that is dependent on von **Willebrand** factor (vWF) is important in the thrombogenesis that occurs under conditions of high shear stress, eg, during acute coronary syndromes (ACSs). A monoclonal **antibody**, **AJvW**-2, directed against the A1 domain of human vWF specifically blocks the interaction between plasma vWF and platelet glycoprotein (GP) Ib. To evaluate the association between the vWF-GPIb interaction and the enhanced shear-induced platelet aggregation (SIPA) observed in ACSs, we tested the effect of this **antibody** on platelet aggregation. Platelet-rich plasma was prepared from the citrated blood of 12 patients with unstable angina (UAP) and 20 patients with acute myocardial infarction (AMI) who were admitted within 3 hours of the onset of cardiac symptoms and from 18 controls. We observed the following: (1) 1.7-fold higher plasma levels of vWF and ristocetin cofactor activity in UAP patients and (2) 2.8-fold higher levels in the AMI group than in controls. Using a cone-and-plate viscometer, we measured the mean value of SIPA under high-shear conditions (108 dyne/cm2) and found them to be 1.3-fold higher in the UAP group and 2.0-fold higher in the AMI group than in controls. The high SIPA in all groups was completely inhibited by 10 mug/mL **AJvW**-2. Under low-shear conditions (12 dyne/cm2), platelet aggregation was increased only in the AMI group, but this was unaffected by **AJvW**-2. We observed a significant correlation in both ACS groups between high SIPA and the plasma vWF level or vWF larger multimers. These findings suggest that the vWF-GPIb interaction is important in coronary occlusion

and that inhibition of this interaction (with the use of **AJvW**-2) may prevent further events in the coronary arteries.

4/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11307463 BIOSIS NO.: 199800088795
Antagonism of vWF inhibits both injury induced arterial and venous thrombosis in the hamster.
AUTHOR: Yamamoto Hiroshi; Vreys Ingrid; Stassen Jean Marie; Yoshimoto Ryota ; Vermylen Jos; Hoylaerts Marc F(a)
AUTHOR ADDRESS: (a)Cent. Mol. Vasc. Biol., Kathol. Univ. Leuven, Campus Gasthuisberg, O and N, Herestr. 49, B-3000 **Belgium
JOURNAL: Thrombosis and Haemostasis 79 (1):p202-210 Jan., 1998
ISSN: 0340-6245
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: von **Willebrand** factor (vWF) is instrumental in arterial but has also been implicated in venous thrombogenesis. To address its role in venous thrombosis, experimental thrombosis was induced in the carotid artery and the femoral vein of hamsters, following which thrombus prevention by two different antagonists of vWF was studied. The first antagonist was the anti-human vWF monoclonal **antibody AJvW**-2, which inhibits the botrocetin and ristocetin induced aggregation of human blood platelets. **AJvW**-2 reacts with an epitope present in the A1 domain of vWF in very different species (human, pig, rabbit, dog, Guinea pig and rat). This epitope was found to be conformational and overlapping with vWF binding sites for aurin tricarboxylic acid (ATA), but not for botrocetin and heparin. **AJvW**-2 has affinities for vWF in the absence (Kd = 0.5 +- 0.03 nmol/l in solution) and in the presence of shear stress (Kd = 3.3 +- 0.6 nmol/l during perfusion at 1,300 s-1 over subendothelial matrix associated vWF) sufficiently elevated to neutralize vWF. During perfusion of subendothelial matrix with anticoagulated human blood, the surface covered by adhering platelets was reduced by **AJvW**-2, with IC50s equal to 6.6 +- 0.34 pg/ml at 1,300 s-1 and to 1 +- 0.01 mug/ml at 2,700 s-1. As a second antagonist, molecular size gel filtered ATA was selected. Fractionated ATA inhibited platelet adhesion to matrix with IC50s equal to 0.27 +- 0.09 mmol/l at 1,300 s-1 and 0.16 +- 0.008 mmol/l at 2,700 s-1. When administered to hamsters, **AJvW**-2 prevented thrombosis in the injured carotid artery dose-dependently (ED50 = 0.15 +- 0.01 mg/kg). Thrombosis in the similarly injured femoral vein was however also inhibited (ED50 = 0.37 +- 0.06 mg/kg). Likewise, fractionated ATA completely inhibited carotid artery thrombosis (ED50 = 0.42 +- 0.13 mg/kg), but also interfered with femoral vein thrombosis (apparent ED50 between 2 and 3 mg/kg). We conclude that antagonizing the vWF A1 domain by **AJvW**-2 and to a lesser extent also by fractionated ATA, inhibits thrombosis not only in the arterial but also in the venous circulation. Since venous thrombi were prevented at only 3-5-fold higher doses of antagonist, vWF participates in injury induced venous thrombosis.

4/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11169585 BIOSIS NO.: 199799790730
Prevention of arterial thrombosis using a novel heparin with enhanced antiplatelet activity and reduced anticoagulant activity.
AUTHOR: Poletti Lawrence F; Bird Karyn; Harris Robert B; Marques Dalila;

Sobel Michael(a)
AUTHOR ADDRESS: (a)MCV, Box 980108, Richmond, VA 23298**USA
JOURNAL: Journal of Vascular Surgery 26 (3):p366-372 1997
ISSN: 0741-5214
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose: Thrombosis after arterial injury is often initiated by von **Willebrand** factor (vWF)-dependent platelet accumulation. A promising antithrombotic strategy is the interruption of platelet/vWF interactions. Previously, we demonstrated how chemical and affinity modification can enhance heparin's anti-vWF activity while reducing conventional anticoagulation. Here, we investigated whether a modified heparin can block platelet-dominated arterial thrombosis. Methods: Standard heparin was oxidized with periodate, refined to have high vWF affinity and inhibitory potency, and tested in a guinea pig model of platelet-dependent arterial thrombosis. In this model, a controlled mechanical arterial injury yields cyclic flow variations (CFVs) caused by recurrent accumulation of platelet thrombi. Results: All six control animals developed CFVs (mean, 10.4 +- 2.6 CFVs), and six of seven animals treated with standard heparin also developed CFVs (mean, 7.6 +- 4.6). Only one of six animals treated with the anti-vWF heparin and one of six treated with **AJvW**-2 (an anti-vWF **antibody**) developed CFVs (mean, 2.0 +- 4.9 and 0.5 +- 1.2, respectively). Thus both the modified heparin and **AJvW**-2 were more effective than standard heparin (p lt 0.03). Bleeding times and platelet counts were unaffected. A modified activated partial thromboplastin time was less prolonged by the modified high-affinity heparin (91 +- 17 seconds) than by standard heparin (144 +- 30 seconds; p lt 0.01). Conclusions. The modified heparin with high vWF affinity was a more effective arterial antithrombotic agent, with fewer conventional anticoagulant effects than standard heparin. Interruption of the vWF/platelet interaction is a promising antithrombotic strategy that may be met by novel heparin-based antithrombotic drugs.

4/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11126919 BIOSIS NO.: 199799748064
Anti-thrombotic effects and bleeding risk of **AJvW**-2, a monoclonal **antibody** against human von **Willebrand** factor.
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JOURNAL: British Journal of Pharmacology 122 (1):p165-171 1997
ISSN: 0007-1188
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 1. A murine anti-human vWF monoclonal **antibody**, **AJvW** -2, was developed that inhibited the interaction between platelet glycoprotein Ib (GPIb) and von **Willebrand** factor (vWF) during the ristocetin- (IC-50 = 0.7 +- 0.1 mu-g ml-1) and botrocetin- (IC-50 = 1.8 +- 0.3 mu-g ml-1) induced aggregation of human platelets. 2. **AJvW**-2 inhibited the high shear stress (10.8 N m-2) induced aggregation of human platelets dose-dependently with an IC-50 = 2.4 +- 0.3 mu-g ml-1, but had no effect on low shear stress induced platelet aggregation (1.2 N m-2) up to 100 mu-g ml-1. 3. **AJvW**-2 also inhibited the high shear stress (5.0 N m-2) induced adhesion of human platelets to collagen I with the same efficacy (IC-50=2.4 +- 0.3 mu-g ml-1), but had no effect at low shear conditions (1.5 N m-2). 4. **AJvW**-2 inhibited the botrocetin-induced aggregation of platelets from guinea-pig, rat, rabbit,

dog and pig at the same concentration range as human platelets; it likewise also inhibited the high shear stress induced aggregation and adhesion to collagen I of guinea-pig platelets. 5. **AJvW**-2 prevented arterial thrombus formation in guinea-pigs at a dose of 100 mu-g kg-1 without prolonging the template bleeding time, whereas the GPIIb/IIIa antagonist lamifiban mediated inhibition of thrombosis at 1000 mu-g kg-1 was accompanied by a significant prolongation of the bleeding time. 6. These results suggest that **AJvW**-2 is a potent inhibitor of the GPIb-vWF interaction and a potential novel antithrombotic agent with lower bleeding risk than GPIIb/IIIa antagonists.

4/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10969235 BIOSIS NO.: 199799590380
Von **Willebrand** factor binds to native collagen VI primarily via its A1 domain.
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JOURNAL: Biochemical Journal 324 (1):p185-191 1997
ISSN: 0264-6021
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Collagen VI is abundant in the arterial subendothelium. To investigate its mechanism of interaction with von **Willebrand** factor (vWF), collagen VI was isolated from human placenta and from the extracellular matrix of the human lung fibroblast cell line MRC-5. Purified vWF bound to non-digested collagen VI with moderately high affinity (EC-50 apprxeq 5 nM) and could be inhibited by the Hirudo medicinalis collagen inhibitor calin. The anti-(human vWF A1 domain) monoclonal **antibody** (**AJvW**-2), as well as aurin tricarboxylic acid (ATA), at concentrations that saturate the vWF A1 domain, also inhibited this binding. In contrast, the monoclonal anti-(human vWF A3 domain) **antibody** (82D6A3) inhibited vWF binding to collagens I, III and IV, but had no effect on vWF binding to collagen VI. Likewise, vWF binding to collagen VI was not inhibited by the recombinant vWF domain D4. Polyclonal anti-(collagen VI) **antibodies**, specifically neutralizing the binding of vWF to collagen VI, confirmed that in the intact endothelial cell extracellular matrix, collagen VI was accessible for interaction with vWF. This binding was only marginally affected by 82D6A3 but was dose-dependently inhibited by **AJvW**-2, ATA and the A1 domain analogue VCL (recombinant A1 domain of vWF), with IC-50 values comparable to those found for the inhibition of vWF binding to isolated collagen VI. The weak interaction of isolated human platelets with collagen VI was mediated via the platelet collagen receptor (GPIa/lIa) and was competitively inhibited by vWF but not by VCL, suggesting that vWF and GPIa/IIa bind to neighbouring but distinct sites on collagen VI. We conclude that vWF binds to collagen VI primarily via its A1 domain, which distinguishes it from the vWF A3 domain-mediated binding to fibrillar collagens.

4/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10731725 BIOSIS NO.: 199799352870
Anti-von **Willebrand** factor **antibody AJvW**-2 specifically inhibits arterial but not venous thrombosis in the hamster.

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JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p172A 1996
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

4/7/14 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

12024659 EMBASE No: 2003129256
The role of VWF-collagen interaction in acute platelet thrombus formation
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Drugs of the Future (DRUGS FUTURE) (Spain) 01 JAN 2003, 28/1 (61-67)
CODEN: DRFUD ISSN: 0377-8282
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 61

The first step in the formation of an arterial platelet thrombus consists of the interaction between collagen-bound VWF and the platelet glycoprotein Ib/IX/V complex. This event results in a further interaction of the collagen receptors with the damaged vessel wall, leading to platelet activation and platelet aggregation, a process mediated by the platelet GPIIb/IIIa receptor. Current antiplatelet agents interfering with platelet activation steps (e.g., acetylsalicylic acid, clopidogrel) or blocking the GPIIb/IIIa receptor (e.g., abciximab, eptifibatide, lamifiban, tirofiban) have proven their clinical usefulness. However, their efficacy is not optimal and therefore the search for new antiplatelet drugs continues. Here we review data on a new approach for preventing arterial thrombosis, i.e., by blocking the initial platelet adhesion step. The in vitro and in vivo antithrombotic effects of inhibiting collagen-VWF binding are summarized and the anticipated benefits of specifically interfering with this interaction are highlighted.

4/7/15 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

11121154 EMBASE No: 2001134903
Anti-human vWF monoclonal **antibody**, **AJvW**-2 Fab, inhibits repetitive coronary artery thrombosis without bleeding time prolongation in dogs
Kageyama S.; Yamamoto H.; Nakazawa H.; Yoshimoto R.
Dr. H. Yamamoto, Developmental Research Laboratories, Pharmaceutical Research Laboratories, Ajinomoto Co., Inc., 1-1 Suzuki-cho, Kawasaki-shi, Kanagawa 210-8681 Japan
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Thrombosis Research (THROMB. RES.) (United Kingdom) 01 MAR 2001, 101/5 (395-404)
CODEN: THBRA ISSN: 0049-3848
PUBLISHER ITEM IDENTIFIER: S0049384800004308
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 28

The antithrombotic and antihaemostatic effects of the monoclonal **antibody** against human vWF (**AJvW**-2 Fab) were investigated in comparison with those of the monoclonal **antibody** against platelet GPIIb/IIIa (abciximab) in dogs. The ex vivo platelet aggregation and template bleeding time were measured before, 5, 90, 210 min and 24 h after injection of either **AJvW**-2 Fab or abciximab in anesthetized beagle dogs. Plasma concentration, vWF occupancy and plasma vWF antigen level were also measured by ELISA. In addition, the antithrombotic effect was evaluated in a canine model of repetitive coronary thrombosis (Folts model). **AJvW**-2 Fab significantly inhibited the ex vivo botrocetin-induced platelet aggregation at 0.18 mg/kg (53% plasma vWF occupancy) and also inhibited cyclic flow reductions (CFRs) at 0.06 mg/kg (31% occupancy). A significant prolongation of the bleeding time was observed at 1.8 mg/kg (95% occupancy), which was 30 times as high as the antithrombotic effective dose. Whereas, abciximab significantly inhibited both the ex vivo ADP-induced platelet aggregation and CFRs at 0.8 mg/kg, which was the minimally effective dose, also resulting in a significant prolongation of the bleeding time. These results suggest that blockade of the GPIb-vWF axis with **AJvW**-2 Fab leads to the inhibition of thrombus formation in the stenosed coronary arteries without less bleeding time prolongation than the GPIIb/IIIa blockade with abciximab. (c) 2001 Elsevier Science Ltd.

4/7/16 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

11077490 EMBASE No: 2001092549
Erratum: Anti-human von **Willebrand** factor monoclonal **antibody** **AJvW**-2 prevents thrombus depodition and neointina formation after ballon injury in guinea pigs (Arteriosclerosis, Thrombosis, and Vascular Biology (2000) 20 (2303-2308))
Arteriosclerosis, Thrombosis, and Vascular Biology (ARTERIOSCLER. THROMB. VASC. BIOL.) (United States) 2001, 21/3 (466)
CODEN: ATVBF ISSN: 1079-5642
DOCUMENT TYPE: Journal ; Erratum
LANGUAGE: ENGLISH
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